Chapter 15

Disease and Therapy: A Role for Oxidants

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1. Introduction

Oxidative stress is a large increase reduction potential in cell or a decrease in reducing capacity of the cellular redox couples such as glutation. Effects of oxidative stress depend on the magnitude of these changes, if the cell is able to overcome small perturbations and regain its original state. However, severe oxidative stress can cause cell death and even moderate oxidation can trigger apoptosis, whereas if it is too intense can cause necrosis.

A particularly destructive aspect of oxidative stress is the production of reactive oxygen species, which include free radicals and peroxides. Some of the less reactive species (superoxide) can be converted by a redox reaction with transition metals or other compounds quinines redox cycle, more aggressive radical species which can cause extensive damage cellular. Most of these species derived from oxygen are produced at a low level in normal aerobic metabolism and the damage they cause to cells is constantly repaired. However, under the severe levels of oxidative stress that causes necrotic damage produces ATP depletion prevents cell death by apoptosis control.

The antioxidants are substances that may protect your cells against the effects of free radicals. Free radicals are molecules produced when your body breaks down food, or by environmental exposures like tobacco smoke and radiation. Free radicals can damage cells, and may play a role in heart disease, cancer and other diseases.

Antioxidant substances include beta-carotene, lutein, lycopene, selenium, vitamin A; and vitamin C. Antioxidants are found in many foods. These include fruits and vegetables, nuts, grains, and some meats, poultry and fish.

Free radicals damage may lead to cancer. Antioxidants interact with and stabilize free radicals and may prevent some of the damage free radicals might otherwise cause.

Studies in cancer cells *in vitro* and *in vivo* animal's models suggest that the use of free radicals decreases the growth of malignant cells. However, information from recent clinical trials is less clear. In recent years, large-scale, randomized clinical trials reached inconsistent conclusions.

Clinical trials published in the 1990s reached differing conclusions about the effect of antioxidants on cancer. The studies examined the effect of beta-carotene and other antioxidants on cancer in different patient groups. However, beta-carotene appeared to have different effects depending upon the patient population, therefore it is important to personalize treatment, and we must take into account the variability to treatment and individualize or personalize therapy. Studies made by Blot WJ et al., in 1993 for the treatment of cancer published in Chinese Cancer Prevention Study, investigated the effect of a combination of beta-carotene, vitamin E, and selenium on cancer in healthy Chinese men and women at high risk for gastric cancer. The study showed a combination of beta-carotene, vitamin E, and selenium significantly reduced incidence of both gastric cancer and cancer overall.

A 1994 cancer prevention study entitled the Alpha-Tocopherol (vitamin E)/ Beta-Carotene Cancer Prevention Study (ATBC) demonstrated that lung cancer rates of Finnish male smokers increased significantly with beta-carotene and were not affected by vitamin E. Epidemiologic evidence indicates that diets high in carotenoid-rich fruits and vegetables, as well as high serum levels of vitamin E (alpha-tocopherol) and beta carotene are associated with a reduced risk of lung cancer. Another study made by Omenn GS in 1994, the Beta-Carotene and Retinol (vitamin A). Efficacy Trial (CARET) also demonstrated a possible increase in lung cancer associated with antioxidants.

The 1996 Physicians' Health Study I (PHS) found no change in cancer rates associated with beta-carotene and aspirin taken by U.S. male physicians.

The 1999 Women's Health Study (WHS) made by Lee IM, tested effects of vitamin E and beta-carotene in the prevention of cancer and cardiovascular disease among women age 45 years or older. Among apparently healthy women, there was no benefit or harm from beta-carotene supplementation. Investigation of the effect of vitamin E is ongoing.

Three large-scale clinical trials continue to investigate the effect of antioxidants on cancer. The Women's Health Study (WHS) is currently evaluating the effect of vitamin E in the primary prevention of cancer among U.S. female health professionals age 45 and older.

In 2006, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) is taking place in the United States, Puerto Rico, and Canada. SELECT is trying to find out if taking selenium and/or vitamin E supplements can prevent prostate cancer in men age 50 or older. Also the experimental and epidemiologic investigations suggest that alpha-tocopherol (the most prevalent chemical form of vitamin E found in vegetable oils, seeds, grains, nuts, and other foods) and beta-carotene (a plant pigment and major precursor of vitamin A found in many yellow, orange, and dark-green, leafy vegetables and some fruit) might reduce the risk of

cancer, particularly lung cancer. The initial findings of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) indicated, however, that lung cancer incidence was increased among participants who received beta-carotene as a supplement. Similar results were recently reported by the Beta-Carotene and Retinol Efficacy Trial (CARET), which tested a combination of beta-carotene and vitamin A.

The Physicians' Health Study II (PHS II) is a follow up to the earlier clinical trial by the same name. The study is investigating the effects of vitamin E, C, and multivitamins on prostate cancer and total cancer incidence. In another case the supplementation with alpha-tocopherol or beta-carotene does not prevent lung cancer in older men who smoke. Beta-Carotene supplementation at pharmacologic levels may modestly increase lung cancer incidence in cigarette smokers, and this effect may be associated with heavier smoking and higher alcohol intake.

Antioxidants neutralize free radicals as the natural by-product of normal cell processes. Free radicals are molecules with incomplete electron shells which make them more chemically reactive than those with complete electron shells. Exposure to various environmental factors, including tobacco smoke and radiation, can also lead to free radical formation. In humans, the most common form of free radicals is oxygen. When an oxygen molecule (O_2) becomes electrically charged or “radicalized” it tries to steal electrons from other molecules, causing damage to the DNA and other molecules. Over time, such damage may become irreversible and lead to disease including cancer. Antioxidants are often described as “mopping up” free radicals, meaning they neutralize the electrical charge and prevent the free radical from taking electrons from other molecules.

Because of the importance that involves using antioxidants as an alternative in the treatment and prevention of chronic degenerative diseases is useful to express the potential in the use and development of new drugs that include antioxidants.

Free radicals are highly reactive chemical species that possess an unpaired electron. Due to it is reactivity, the radicals react readily with other molecules. When free radicals come into contact with the molecules of the human body such as proteins, lipids, carbohydrates, DNA nucleic acids, react with them. These reactions cause changes in the normal functions of these primary metabolites, which cause severe damage that can cause diseases such as cancer and degenerative diseases like Parkinson´s disease or Alzheimer´s disease and atherosclerosis, coronary heart disease and diabetes [1-4].

When any of these afore mentioned diseases, the patient receive the treatment used to treat the particular disease, however, prevention plays a big role. Oxidation in the body tissues caused by free radicals can be prevented with a daily intake of foods that have antioxidants.

The implications of modern life cause changes in eating habits of people, these results in a lack of antioxidants in the body to cope with free radicals that are in contact. The role of antioxidants is to react with free radicals and thus prevent, to react with the primary metabolites, thus acting as natural shields against diseases like cancer [5, 6].

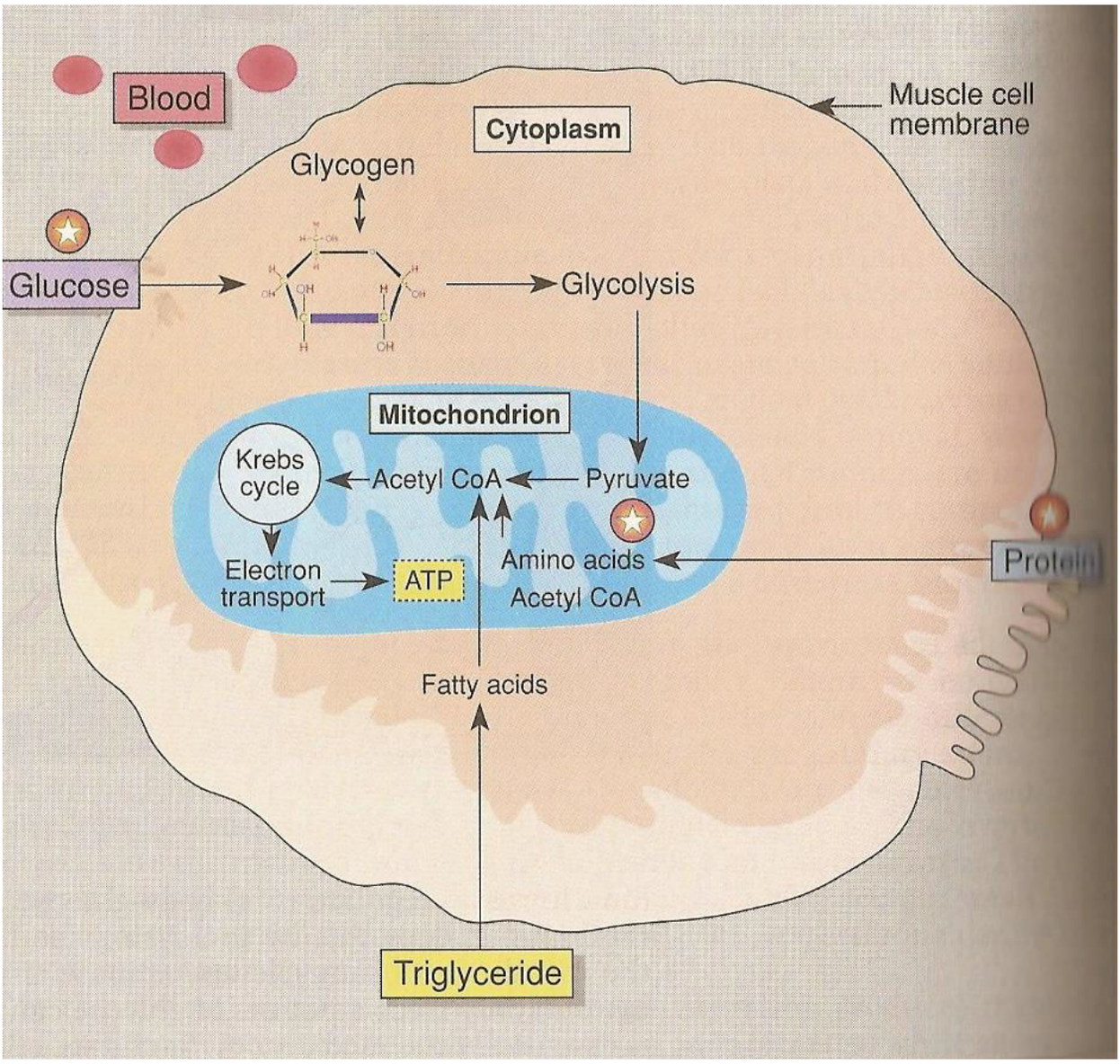

Figure 1. Antioxidants decrement oxidative processes. [Bruce Ames Ph.D., University of California Lecture U.C.T.V. viewed on 08-14-2004].

2. Cancer

2.1. Breast cancer

Currently breast cancer is a disease of high incidence worldwide and causes millions of deaths annually [7]. In the treatment of various cancers have been used drugs that originate from natural products. To get to the application of the drug as a treatment, it requires years of research. The use of treatment leads to the destruction of cancer cells and normal cells in addition, there are numbers side effects resulting from the application of therapies. Preven-

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tion of disease is certainly a great alternative to the aggressive use of medications commonly used. The simplest method to prevent cancer and other diseases is undoubtedly add to the diet foods that contain high concentrations of antioxidants, this treatment is easy to perform and causes no adverse side effects. Other organisms containing large amounts of secondary metabolites some of which can act as antioxidants and thereby help prevent cancer and prevent its development (Fruits, vegetables, plants).

Antioxidants can act in two ways:

Blocking cancer, in the initial stage protecting cells against oxidative species and enhancing DNA repair.

Suppressing cancer by inhibiting the progressive stages after formation of pre-neoplastic cells [8].

Studies are underway to help better understand the mechanism of action of antioxidants and test its efficacy against cancer and other diseases. Several studies report that the addition to the diet of foods containing antioxidants may increase the effectiveness of cancer treatment, and help strengthen the body against the side effects associated with treatment [9-11]. The antioxidants found in fruits and vegetables can mention vitamins C and E, carotenoids group and the group of polyphenols. Polyphenols are a group of antioxidant flavonoids to which they belong. There are several types of flavonoids and can be found in foods such as blackberries, blueberries, strawberries, plum, peach, apple, tomato, cherry, broccoli, onion, soya been, legumes like green gram, lupine peas, soy beans, white and horse gram, green leafy spices, citrus fruits, tea, red grapes, chocolate, cocoa and red wine beverages [12].

The following briefly discuss some results of studies using antioxidants from fruits and vegetables for the treatment of breast cancer.

Research conducted in Canada by Hakimuddin and colleagues [13] showed that the polyphenols found in red wine have selective toxicity against MCF-7 cell type of breast cancer; the authors indicate the importance of a diet that incorporates red wine and feeding grapes to serve as a preventive strategy against cancer, which also can be combined with standard therapies.

As mentioned above plums and peaches are fruits that contain phenolic compounds. In a study to test the activity of phenolic species as cancer chemopreventive agents present in extracts of plums and peaches, we found that peaches and plums contain a mixture of phenolic compounds with the ability to inhibit cell lines MCF-7 and MDA -MB435. A very important point to consider is that phenolic acids were isolated chlorogenic and neo-chlorogenic which have great potential for use as chemopreventive agents exerting growth inhibition of the cell line MDA-MB-435 and low toxicity to the normal cell line MCF-10A [14].

Another recent study [15], focused on the action of terpenes located in the skin of the olives suggests that they may serve as natural potential protective against breast cancer. The triterpenes were isolated in significant quantities from the pulp of the olive oil and can act prophylactically and therapeutically.

Currently the investigation for the treatment of breast cancer using apigenin, a flavonoid found in celery. The study conducted at the University of Missouri (United States) [16] was performed in mice that were implanted cell line BT-474, of rapid growth. Mice were also treated with medroxyprogesterone acetate (MPA), which is used in postmenopausal women. Another group of mice was used as a blank. The group of mice treated with MPA was injected apigenin, found that cancerous tumors grew rapidly in mice that were treated with apigenin. Moreover, in mice treated with apigenin was observed a decrease of the tumor when compared with the group of mice used as a blank. Yet unknown mechanism of action of apigenin chemical, however, although the study was conducted in mice, is very promising for future treatment of breast cancer.

2.2. Prostate cancer

Prostate cancer is a very common type of cancer afflicting men; it is now easy detection by prostate specific antigen test (PSA for its initials in English) [17]. Which are still unknown factors that cause this type of cancer, the disease also takes years in some cases to express symptoms, making it necessary for men to undergo regular medical examinations to detect early. One form of treatment of prostate cancer is surgery, whereby the prostate is removed, but this is a procedure which results in urinary incontinence and impotence, which in some cases is permanent.

Prevention through diet prostate cancer has increased because it is recognized as a way to combat this disease [18, 19]. Among the foods that are recommended for the prevention of prostate cancer are generally fruits and vegetables due to its high content of antioxidants. Fruits like pomegranate containing metabolites such as polyphenols and delphinidin urolitina A and B chloride, kaempferol, and punicic acid are considered biologically active against prostate cancer [20, 21].

Other fruit that contains a variety of polyphenolic compounds is strawberry [22] has been found that extracts of strawberry juice cell lines tested against prostate cancer proved effective as antiproliferative agents, is also noteworthy to mention that were tested individually some of the individual components of the extract (cyanidin-3-glucoside, pelargonidin, pelargonidin-3-glucoside, pelargonidin-3-rutinoside, kaempferol, quercetin, kaempferol-3-(6'-coumaroyl) glucoside, 3,4,5 trihydroxyphenyl-acrylic acid-, glucose ester of (E)-*p*-coumaric acid, and ellagic acid) which also showed efficacy individually [23]. These studies confirm the effectiveness of the cutter to inhibit growth of cancer cells.

The apple is considered the quintessential fruit of health, its daily intake is associated with low risk of chronic diseases and cancer, particularly prostate and colon [24-26]. The block contains a variety of compounds polyphenolic that are responsible for their biological activity among these compounds, studies were performed with quercetin which has proven effective as an inhibitor *in vitro* cell growth of prostate cancer [23, 24]. Another study showed that the antioxidant activity of apples is correlated [27] with the total concentration of phenolic compounds present in it clear that this concentration varies according to growing region, and other growth period factors [28-30]. The tomato is another fruit with high antioxidant capacity and owes its activity to lycopene, a carotenoid, which gives the charac-

teristic red color to the fruit [31, 32]. It has been reported that tomato consumption reduces the occurrence of prostate cancer [33-35].

Another study used extracts of potato species Solanum jamesii to test their cytotoxic activity toward antiproliferatva and prostate cancer cells and colon *in vitro*. The extracts were found to inhibit proliferation of cancer cells PC-3 prostate as well as in colon cancer cells LNCaP. Fractions were also tested extract containing anthocyanin and it showed the same activity as the full extract [36].

2.3. Cervical cancer

It is a type of cancer that has one of the top female deaths worldwide [37]. Its main cause is due to Human Papilloma Virus, which is a group of more than 150 types of viruses and is transmitted by sexual contact [38]. To the treatment of cervical cancer, chemotherapy and radiation therapy is performed. As prevention against this type of cancer was recommended not realize sexual contact with infected persons. Another form of prevention is the application of the vaccine that protects against types of HPV high risk of developing cancer. These vaccines Gardasil ® and Cervarix ® were approved by the Federal Drug Administration (FDA) of EU, but these vaccines are only for women, 9 to 26 years of age who are not infected by the virus.

Another recommendation to prevent this cancer is to stimulate the immune system by eating foods rich in antioxidants, because if the body is weakened, the virus is an opportunity to attack and develop cancer [38]. Have also been performed *in vitro* studies to observe foods as antioxidants influence on the growth of cervical cancer cells [39]. One study was carried out with extracts of different types of berries and tested for anti-proliferative activity on HeLa cells (cervical carcinoma). The results show that extracts from blueberry and pomegranate have little effect inhibiting the growth of HeLa cells. The most effective extracts with increasing concentration were: strawberry extract, arctic bramble, lingonberry and cloudberry. It has also been reported [40] that glycoalkaloids present in commercial potatoes inhibit the growth of different types of cancer cell lines, including HeLa cervical cancer cells.

In therapy of cancer selenium doses is 4000 μg in continuous infusion of 1000 μg/9 days, total: 13 mg [41] (Forceville et al, 2007), i.v. bolus 1000 μg in 30 minutes for continuous infusion 1000 μg/d 14 d, total: 15 mg; i.v. bolus 2000 μg in 2 hours continuous infusion 1600 μg/d, 10 d, total 18 mg [42].

3. Diabetes

Diabetes is a metabolic disorder associated with defects in secretion and insulin action [43]. Type 1 diabetes also known as insulin dependent and type 2 diabetes called non-insulin dependent. Both conditions are associated with the formation of free radicals that cause oxidative stress and disease manifestation. Diabetes is associated with health problems such as neuropathy, retinopathy, erectile dysfunction in men, kidney problems, healing and more

[44, 45]. Because diabetes is a disease of oxidative stress, it is expected that the antioxidants in fruits, vegetables and plants to help combat it.

Several studies report that a proper diet that includes antioxidants is important to reduce the risk of diabetes. We have found that various antioxidants present in some foods and plants as coumarins, some terpenes, flavonoids, lignans, phenylpropanoids, tannins and can help people prevent disease and for helping diabetics [46, 47]. These substances exert their activity by inhibiting the action of R-amylase enzyme. Amylase is an enzyme produced in the pancreas and salivary glands; their function is to help the digestion of carbohydrates [48]. Among the flavonoids that can inhibit R-amylase are the quercetin, myricetin, epigallocatechin gallate, and cyanidin. Tannins, present in green and black teas, grapes, wine, raspberry, and strawberry, also seem to be good R-amylase inhibitors. Among fruits and vegetables reported with inhibitory capacity toward the R-amylase in vitro are the red grapes, strawberry, raspberry and, green pepper, broccoli, ginger, and carrot [49-54].

Thanks to these findings, it has been proposed the use of some natural metabolites present in these fruits for the control of hyperglycemia following ingestion of food. The advantage of these natural metabolites is that its use can avoid the side effects that occur when drugs are used for this purpose [55, 56].

Consumption of foods rich in antioxidants can also prevent the complications of this disease has recently been shown that biotin is a vitamin which is part of the B vitamins, which can be found in foods such as biotin find when we eat certain vegetables: cauliflower, peanut butter, mushrooms, yeast, potatoes, mushrooms, almonds, walnuts, soybeans, chickpeas, grapes, strawberries, watermelon, bananas, wheat, flour, pasta, bread, oats, rice, liver, yolk egg, kidney, fish, poultry and offal in general, can help improve metabolism and insulin sensitivity, leading to decreased levels of blood sugar, also sold capsules containing biotin [57, 58].

Resveratrol is a polyphenol present in red wine. According to research Medical Center, University of Texas Southwestern in the U.S. [60], resveratrol administered directly into the brain of diabetic mice, can help control type two diabetes by improving blood sugar levels. What makes the resveratrol is to activate a protein called sirtuin which is expressed in parts of the brain that govern the metabolism of glucose. Much remains to be investigated but it is certainly likely that the intake of red wine under medical supervision can help control diabetes.

Also been studied antioxidants in plants and animals such as the following examples show.

A group of researchers at the University of Jaen in Spain isolated a compound called Cinnamtannin B-1 of the laurel, which has antioxidant properties that can eliminate free radicals that cause diseases such as diabetes. The university has signed an agreement with a pharmaceutical for the distribution of this antioxidant [61].

Lipoic acid, also known as alpha lipoic acid or thioctic acid, is produced in small quantities our bodies, it participates in the metabolism significantly. Can also be found in foods like red meat, yeast and some vegetables such as spinach, broccoli.

In this fatty acid properties are attributed as an antioxidant par excellence also can help reuse of other antioxidants like vitamins C and E, glutathione and coenzyme Q10. Among the many properties that are attributed to reduction of varicose veins, skin moisture, enhances energy levels in the body, cancer protection among others.

Also attributed the reduction in blood glucose levels for type 2 diabetes and help combat the discomforts caused by peripheral neuropathy, and therefore coupled with the effects mentioned above, this antioxidant is ideal for diabetics [62-67].

Currently sold in different forms under different names, but the diabetic patient can take doses of lipoic acid consuming identified through the diet. No indication that lipoic acid has contraindications, although high doses can cause episodes of hypoglycemia [68].

4. Arteriosclerosis

Arteriosclerosis is the hardening of the arteries due to fat accumulation; this may lead to a heart attack that can end life [69]. Atherosclerosis is a preventable disease with a balanced diet and exercise. The diet should include variety of fruits and vegetables and be low in fat. Antioxidants play an important role in preventing this disease, it is known that there is a relationship between red wine consumption and the low incidence of cardiovascular disease; this is due to the action of the antioxidants present in grapes. We recommend a daily intake of 375 mL of red wine to increase levels of high density lipoprotein HDL proteins, ie proteins responsible for transporting fat [70, 71]. Studies with another fruits can be determining its effectiveness in the prevention of arteriosclerosis.

Another fruit that has been investigated for its antioxidant and cardiovascular protective effects are blueberries. Studies realized in Arkansas State University, evaluated the effect on two groups of mice for twenty weeks. One group was used as a target, leading a normal diet; the other group was fed a blueberry base [72], found that mice with arterial lesions, a significant percentage decreased injuries, compared with the group of mice that did not eat blueberries. The researchers suggest incorporating blueberries to the diet to improve cardiovascular health and recommended as the ideal fruit for the treatment of hypercholesterolemia.

It is known that fruits such as cranberries have high antioxidant levels and tested their effectiveness in promoting cardiovascular health [73-75]. This study was supplemented to a group of men for two weeks with cranberry juice. Over time he found an increase in plasma antioxidant capacity and a decrease in LDL (low density lipoprotein) in addition to an increase in HDL in obese men. Work is to show whether supplementation based cranberry juice may have the same antioxidant capacity and the same protective benefit as red wine, if so would avoid alcohol.

In another study conducted at the University of Buffalo studied the effect of resveratrol as an antioxidant and its possible use in treating atherosclerosis. In this investigation were not used fruits or vegetables, but was used an extract of the plant. The extract containing resver-

atrol was administered at doses of 40 mg daily to a group of 10 people, another group of 10 people also served as a target. During the six weeks of the study, blood tests were performed on the results; researchers concluded that Polygonum cuspidatum extract has a therapeutic effect against oxidative stress. These results show that resveratrol, as already mentioned above, are effective to counteract the effect of free radicals, and in the case of arteriosclerosis, can also help prevent it [76].

5. Obesity and metabolic syndrome

The metabolic syndrome has been identified as a target for dietary therapies to reduce risk of cardiovascular disease; however, the role of diet in the etiology of the metabolic syndrome is poorly understood. The metabolic syndrome consists of a constellation of factors that increase the risk of cardiovascular disease and type 2 diabetes. The etiology of this syndrome is largely unknown but presumably represents a complex interaction between genetic, metabolic, and environmental factors including diet [77-79]. The studies endothelial function by assessing the vascular responses to L-arginine, the natural precursor of nitric oxide it´s characterized for the low-grade inflammatory state of patients with the metabolic syndrome by measuring circulating levels of high-sensitivity C-reactive protein (hs-CRP) as well as of interleukins 6 (IL-6), 7 (IL-7), and 18 (IL-18). These proinflammatory ILs have been prospectively associated with thrombotic cardiovascular events [80, 81] or have been suggested to be involved in plaque destabilization [82]. The diet designed to increase consumption of foods rich in phytochemicals, antioxidants, α-linolenic acid, and fiber prevent Metabolic Syndrome.

The diet rich in whole grains, fruits, vegetables, legumes, walnuts, and olive oil might be effective in reducing both the prevalence of the metabolic syndrome and its associated cardiovascular risk. One of the mechanisms responsible for the cardioprotective effect of such a diet may be through reduction of the low-grade inflammatory state associated with the metabolic syndrome. Although weight reduction remains a cornerstone of therapy for the metabolic syndrome, from a public health perspective adoption of a diet rich in phytochemicals, antioxidants, α-linolenic acid, and fiber may provide further benefit on cardiovascular risk, especially in patients who do not lose weight.

If antioxidants play a protective role in the pathophysiology of diabetes and cardiovascular disease, understanding the physiological status of antioxidant concentrations among people at high risk for developing these conditions, such as people with the metabolic syndrome, is of interest. However, little is known about this topic. Because the prevalence of obesity, which is associated with decreased concentrations of antioxidants [83], is high among people with the metabolic syndrome, they are probably more likely to have low antioxidant concentrations. Consequently, our purpose was to examine whether concentrations of several antioxidants are lower among those with than those without the metabolic syndrome.

For example a retinol from the liver, the main storage site for retinol is transported to peripheral tissues by retinol binding protein. Retinol may be released as a retinyl ester; howev-

er, when the ability of the liver to store retinol is exceeded or when liver function is impaired [84]. Thus, the higher retinyl ester concentrations among those who did not have the metabolic syndrome may indicate that they consumed larger amounts of vitamin A compared with people who have this syndrome. Our findings may have implications for people with the metabolic syndrome, health care professionals who care for them and researchers who study the metabolic syndrome. People with the metabolic syndrome are at increased risk for diabetes and cardiovascular disease, and a role for oxidative stress in the pathophysiology of these conditions has been postulated. Free radical species is one of the principal mechanisms of action of antioxidants, other mechanisms that affect the pathophysiology of diabetes and cardiovascular disease may be operating as well [83]. The effects of vitamins C and E have received a great deal of interest. Through effects on oxidation of LDL cholesterol concentration, leukocyte adhesion, and endothelial function, vitamins C and E may slow atherosclerosis [86, 87].

6. Liver cirrhosis

Currently the evidence supports the role of nutritional deficiency in Alcoholic Liver Disease (ALD) [88–95]. Lieber and colleagues show that progressive ALD proceeds despite adequate nutrition [96, 97]. The latter hypothesis was based primarily on the observation that baboons fed a nutritionally adequate liquid diet containing ethanol at 50% calories developed nearly the whole spectrum of ALD including cirrhosis. Studies demonstrated profound effects on ethanol-induced liver injury by intake of nutrients such as polyunsaturated fat and iron in quantities that were never thought to be important. The concept of 'sensitization' and 'priming' is currently considered fundamental to our pursuit for elucidation of pathogenetic mechanisms of ALD. The sensitization is a conditioning that makes the target cells, hepatocytes, more vulnerable to harmful effects triggered by ethanol and priming as the effect that promotes specific injurious mechanisms. The sensitizing and priming are rendered by the complex interactions of primary mechanistic factors and secondary risk factors. For example, intake of polyunsaturated fat in ethanol-fed rats, but not in pair-fed controls, results in a synergistic priming effect on induction of cytochrome P4502. E1 (CYP2E1) with consequent oxidative injury to the liver [98]. Conversely, saturated fat prevents this priming effect and abrogates depletion of a mitochondrial pool of glutathione (GSH) [99], one of the most crucial sensitization effects of ethanol on hepatocytes [100]. Iron is another example. Whereas a slight increase in hepatic iron content by dietary iron supplementation is harmless in control rats, it exacerbates alcoholic liver injury via accentuation of oxidative stress [101]. Further, increased iron storage in hepatic macrophages is a potential priming mechanism forenhanced expression of tumor necrosis factor a (TNF-a) in experimental ALD [102] Besides nutritional factors, female gender, age, concomitant intake of other drugs that can induce CYP2E1, hepatitis virus infection, and genetic predisposition are all considered risk factors. Even among the primary mechanistic factors that include acetaldehyde, oxidative stress, immune response, hypoxia, and membrane alterations, there are cross-interactive relationships to render sensitization or priming effects. For instance, acetaldehyde, a potent toxic metabo-

lite of ethanol, induces liver injury via its covalent binding to structural or functional proteins of the cells [103] while promoting oxidative stress via consumption of GSH. In turn, deleterious effects of acetaldehyde-protein adduct formation may be accentuated by oxidative stress since malondialdehyde, a lipid peroxidation end product, can increase the binding affinity of acetaldehyde by 13-fold [104]. The resulting novel hybrid adducts are highly immunogenic and may incite immune response mediated liver injury [105, 106]. Although cellular immune response and inflammation are regarded as independent mechanisms of ALD, they can also lead to oxidative stress via the release of reactive oxygen species (ROS) by NADPH oxidase or action of TNF-a at the electron transport chain in target cells. The multifactorial nature and complex interaction among primary mechanistic factors and between primary and secondary factors appear to be the basis for the heterogeneous response that alcoholics exhibit for ALD. Elucidation of the sensitization and priming mechanisms involving cross-interactions of these factors should allow us to gain insight into the most fundamental question, which is why only a small fraction of alcoholics develop advanced ALD. The experimental models to use for control deletion and addition analyses in order to identify what primary and secondary factors are required for the expression of a particular aspect or whole spectrum of experimental ALD. It is need experts in various disciplines need to work together to provide cutting-edge science for elucidating the precise nature and mechanisms that underlie interactions.

Antioxidants represent a potential group of therapeutic agents for ALD. They likely provide beneficial effects on hepatocytes via desensitization against oxidant stress while inhibiting priming mechanisms for expression of proinflammatory and cytotoxic mediators via suppression of NF-kB [107, 108]. Potential approaches may include cell type-specific targeting of antioxidant therapy and development of modalities for more specific and selective regulation of NF-kB-mediated signaling.

The development of cirrhosis is usually associated with oxidative stress and lipid peroxidation (LPO). Studies in models of cirrhosis to use carbon tetrachloride (CCl_4) inhalation in the rat show several similarities with human cirrhosis. The metabolism of CCl_4 into trichloromethyl (CCl_3•) and peroxy trichloromethyl (•$OOCCl_3$) free radicals has been reported to cause hepatotoxic effects, like fibrosis, steatosis, necrosis, and hepatocarcinoma [109, 111].

Some compounds that have been studied as possible protectors against liver cirrhosis are known for their anti-inflammatory and antioxidant properties. Plants contain numerous polyphenols, which have been shown to reduce inflammation and thereby to increase resistance to disease [112]. Quercetin (Q), a polyphenolic flavonoid compound present in large amounts in vegetables, fruits, and tea, exhibits its therapeutic potential against many diseases, including hepatoprotection and the inhibition of liver fibrosis [113–114]. It contains a number of phenolic hydroxyl groups, which have strong antioxidant activity [116, 117]. The average intake varies between countries but is approximately 23 mg/day [118].

By increasing the endogenous antioxidant defenses, flavonoids can modulate the redox state of organisms. The major endogenous antioxidant systems include superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx), which is essential for the detoxification of lipid peroxides [119-121].

7. Hypertension

Excessive reactive oxygen species (ROS) have emerged as a central common pathway by which disparate influences may induce and exacerbate hypertension. Potential sources of excessive ROS in hypertension include nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mitochondria, xanthine oxidase, endothelium-derived NO synthase, cyclooxygenase 1 and 2, cytochrome P450 epoxygenase, and transition metals. While a significant body of epidemiological and clinical data suggests that antioxidant-rich diets reduce blood pressure and cardiovascular risk, randomized trials and population studies using natural antioxidants have yielded disappointing results. The reasons behind this lack of efficacy are not completely clear, but likely include a combination of [122] ineffective dosing regimens, [123] the potential pro-oxidant capacity of some of these agents, [124] selection of subjects less likely to benefit from antioxidant therapy (too healthy or too sick), and inefficiency of nonspecific quenching of prevalent ROS versus prevention of excessive ROS production. Antioxidants as vitamins A, C and E, L-arginine, flavonoids, and mitochondria-targeted agents (Coenzyme Q10, acetyl-L-carnitine, and alpha-lipoic acid) can be use to treatment hypertension. Currently exist incomplete knowledge of the mechanisms of action of these agents, lack of target specificity, and potential interindividual differences in therapeutic efficacy preclude us from recommending any specific natural antioxidant for antihypertensive therapy at this time.

Reactive oxygen species (ROS) are generated by multiple cellular sources, including NADPH oxidase, mitochondria, xanthine oxidase, uncoupled endothelium-derived NO synthase, cycloxygenase, and lipoxygenase. The dominant initial ROS species produced by these sources is superoxide (O_2^-). Superoxide is short-lived molecule that can subsequently undergo enzymatic dismutation to hydrogen peroxide. Superoxide can oxidize proteins and lipids, or react with endothelium-derived nitric oxide (NO) to create the reactive nitrogen species peroxynitrite. Peroxynitrite and other reactive nitrogen species can subsequently oxidize proteins, lipids, and critical enzymatic cofactors that may further increase oxidative stress [125]. Hydrogen peroxide produced by enzymatic dismutation of O_2^- can be further convert to highly reactive hydroxyl radical (via Fenton chemistry) that can cause DNA damage. The balance between superoxide production and consumption likely keeps the concentration of O_2^- in the picomolar range and hydrogen peroxide in the nanomolar range [126]. These homeostatic levels of reactive oxygen species appear to be important in normal cellular signaling [127-132] and normal reactions to stressors [133, 134].

Randomized trials employing non-pharmacological dietary interventions emphasizing fruits, vegetables, whole grains, and nuts have shown impressive blood pressure lowering results in both hypertensive and normotensive subjects [135, 136]. Similar interventions demonstrated to reduce cardiovascular morbidity and mortality continue to maintain interest in the potential of isolating specific compounds enriched in these diets that may be responsible for the overall dietary benefits [137].

The dietary components in these studies are high in compounds known to have antioxidant properties leading many to ascribe the benefits of these diets to their increased content of

natural antioxidants. However, prior randomized trials and population studies in healthy populations and patients at high risk for cardiovascular events that have employed combinations of some of these natural antioxidants as dietary supplements have, for the most part, shown disappointing results [138-145]. The reasons behind these disappointing results are not completely clear, but likely include a combination of 1) ineffective dosing and dosing regimens 2) the potential pro-oxidant capacity and other potentially deleterious effects of these some of these compounds under certain conditions [146-148], 3) selection of subjects less likely to benefit from antioxidant therapy (too healthy or too sick). Populations at intermediate cardiovascular risk may be better suitable to see effects of antioxidants in shorter term studies [149], 4) inefficiency of non-specific quenching of prevalent ROS versus prevention of excessive ROS production [150, 151].

When considering antioxidant therapy for hypertension, lessons from prior disappointing attempts to reduce blood pressure and cardiovascular risk with antioxidant therapy should be considered. The profile of an ideal agent is outlined in The importance of patient selection is being increasingly recognized in light of emerging data suggesting that antioxidant supplementation in healthy subjects may blunt the protective benefits of aerobic exercise training, suggesting ROS generation can be beneficial under certain circumstances.

Antioxidants neutralize the oxidative processes and modify levels in plasma	
↑ Lipid peroxidation	↑ MDA (TBAR), F2-isoprostane
↑ NO synthesis	↑ Nitrite, nitrate, nitrotyrosine
↓ Circulating antioxidants	↓ Uric acid, protein SH groups, Bilirubin (unconjugated)
	↓ Ascorbic acid, α-tocopherol, β-carotene, lycopene
	↓ Antioxidant enzymes (GSHPx)
	↓ Selenium, zinc
	↓ GSH
Xanthine oxidase activation	↑ Plasma xanthine oxidase

Table 1. Antioxidants neutralize the oxidative processes and modify levels in plasma. [150]

7.1. Antioxidant vitamins

7.1.1. Vitamin A precursors and derivatives

Vitamin A precursors and derivatives are retinoids that consist of a beta-ionone ring attached to an isoprenoid carbon chain. Foods high in vitamin A include liver, sweet potato, carrot, pumpkin, and broccoli leaf. Initial interest in vitamin A-related compounds focused primarily on beta-carotene, given initial promising epidemiological data with respect to its cardioprotective effects and some correlation with higher plasma levels to lower blood pressure in men. However, concerns about beta-carotene's pro-oxidative potential came to light with a report suggesting adverse mitochondrial effects of beta-carotene cleavage products. Further, adverse mortality data with respect to beta-carotene has limited interest in this compound as an effective antihypertensive agent.

Recently, interest in vitamin A derivatives has turned to lycopene, itself a potent antioxidant [152], found concentrated in tomatoes. One small study has shown a reduction in blood pressure with a tomato-extract based intervention (containing a combination of potential anti-oxidant compounds including lycopene) in patients with stage I hypertension, [153] although second study showed no effect in pre-hypertensive patients [154].

7.1.2. Ascorbic acid (Vitamin C)

L-ascorbic acid is a six-carbon lactone and, for humans, is an essential nutrient. In Western diets, commonly consumed foods that contain high levels of ascorbic acid include broccoli, lemons, limes, oranges, and strawberries. Toxicity potential of this compound is low, although an increased risk of oxalate renal calculi may exist at higher doses (exceeding 2 grams/day).

The initial purported mechanisms for the potential benefits of ascorbate supplementation were centered on quenching of single-electron free radicals. Subsequent research has demonstrated that the plasma concentrations of ascorbate required for this mechanism to be physiologically relevant are not attainable by oral supplementation [155]. However, vitamin C can concentrate in local tissues to levels an order of magnitude higher than that of plasma. At this ascorbate may to effectively compete for superoxide and reduce thiols [156]. Recent data also suggest potential suppressive effects of ascorbate on NADPH oxidase activity [157, 158]. Ascorbate appears to have limited pro-oxidant ability. [159].

Ascorbate's anti-hypertensive efficacy has been evaluated in multiple small studies [160-163] but not all, show modest reductions in blood pressure in both normotensive and hypertensive populations. These data also suggest that supplementation has limited effect on systemic antioxidant markers and little additional blood pressure benefits are seen beyond the 500 mg daily dose. Large scale randomized trial data specific to ascorbate supplementation and its effects on hypertension are currently lacking. Data from Heart Protection Study (HPS) suggest no significant mortality from supplementation with 250mg/day of ascorbate supplementation. However, the relatively low dose of ascorbate, use of combination therapy, and high-risk patient population studied in HPS leave unanswered the key ques-

tions of appropriate dosing and target. In the inflammatory processes follow next scheme in the therapy antioxidant [164].

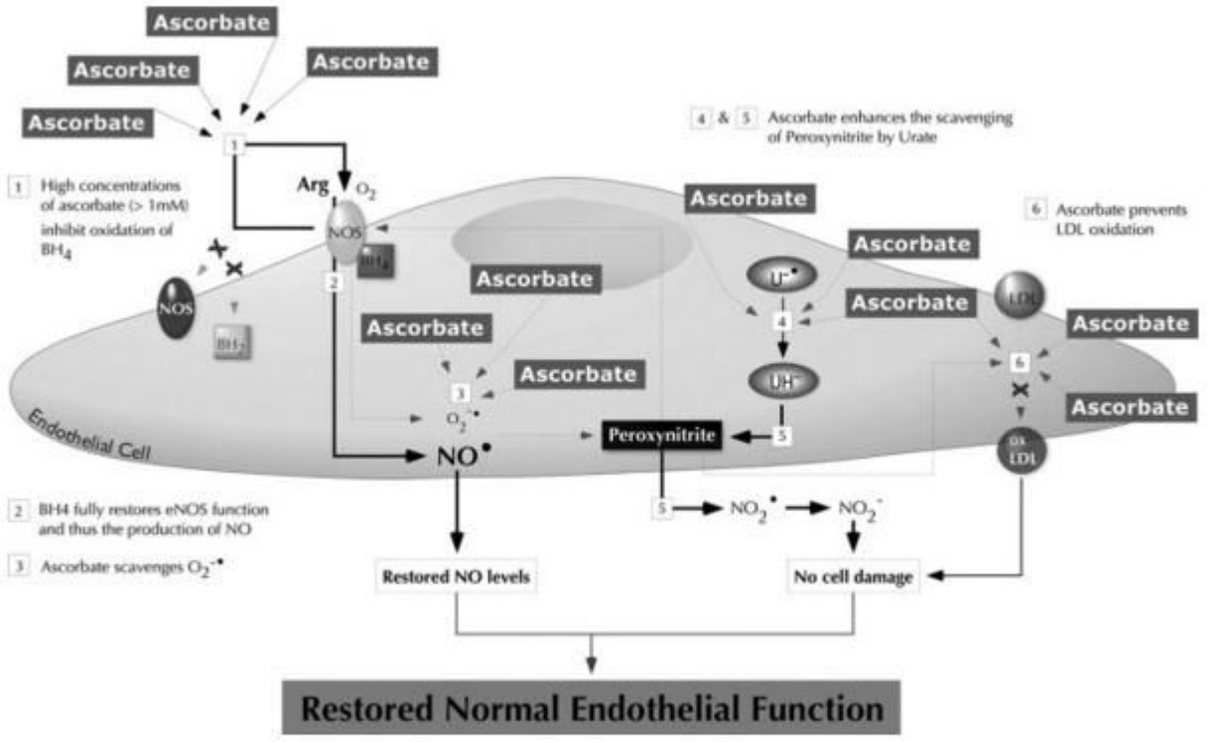

Figure 2. Restored normal endothelial function.

7.1.3. α-Tocopherol (Vitamin E)

Vitamin E is a generic term for a group of compounds classified as tocopherols and tocotrienols [165]. While there are four isomers in each class of Vitamin E compounds, the overwhelming majority of the active form is α-tocopherol. [166, 167]. Dietary sources high in vitamin E include avocados, asparagus, vegetable oils, nuts, and leafy green vegetables.

Vitamin E is a potent antioxidant that inhibits LDL and membrane phospholipid oxidation. Interestingly, inflammatory cells and neurons have binding proteins for α-tocopherol, the actions of which may include inhibition of NADPH oxidase, lipoxygenase, and cyclo-oxygenase, actions which may lower oxidative stress [168]. However, studies demonstrating vitamin E's pro-oxidant capacity under certain cellular conditions suggest that local condition may influence the vitamin E's redox activity [169]. Initial excitement for vitamin E supplementation was based on the reduction of cardiovascular events seen in the CHAOS study. However, follow-up studies have been largely disappointing [170-171]. While one small study that used vitamin E in combination with zinc, vitamin C, and beta-carotene showed a modest, significant reduction in blood pressure over 8 weeks of therapy, other small studies, show either no effect from vitamin E supplementation. Further, the more definitive HOPE

trial, failed to show blood pressure or mortality benefit for patients at high risk for cardiovascular disease [172]. Vitamin E inhibits free radicals reactions.

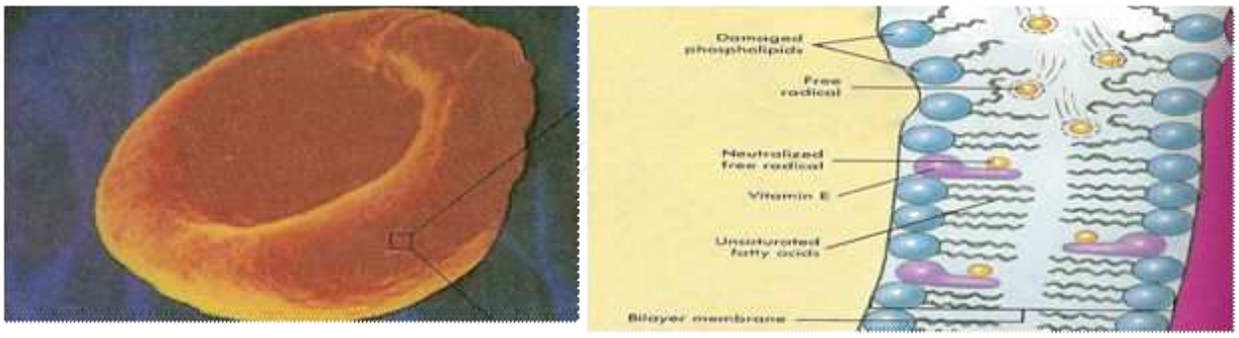

Figure 3. Antioxidants function in the organism.

7.1.4. L-Arginine

L-arginine is an amino acid and the main substrate for the production of NO from eNOS in a reaction that is dependent on tetrahydrobiopterin [173]. Potential dietary sources include milk products, beef, wheat germ, nuts, and soybeans. Reduced levels of tetrahydrobiopterin leads to uncoupling of reduced NADPH oxidation and NO synthesis, with oxygen as terminal electron acceptor instead of L-arginine, resulting in the generation of superoxide by eNOS [174-176]. Low cellular levels of L-arginine have been demonstrated in human hypertension. While L-arginine deficiency itself does not appear to lead to uncoupling of eNOS, [177] low levels of L-arginine may lead to reduced levels of bioavailable NO which could contribute to hypertension. Thus, L-arginine supplementation could theoretically reduce blood pressure by allowing for restoration of normal NO bioavailability, perhaps overcoming overall L-arginine deficiency as well as more successfully competing fo the eNOS active site with circulating asymmetric dimet hylarginine, a circulating competitor of L-arginine that may be increased in the setting of hypertension.

This concept is supported by studies demonstrating the anti-hypertensive effect of L-arginine supplementation in salt-sensitive rats, healthy human subjects, hypertensive diabetics, patients with chronic kidney disease, and diabetic patients in combination with N-acetylcysteine, a precursor of glutathione [178] L-arginine's anti-hypertensive response may be mediated in part by its suppressive effects on angiotensin II and endothelin-1, and its potentiating effects on insulin.

However, recent concerns about potential deleterious increases in homocysteine in the setting of L-arginine supplementation have been raised. The majority of L-arginine is processed into creatine, which leads increased homocysteine levels. Homocysteine can increase oxidative stress. A recent study confirms that this mechanism is relevant to L-arginine metabolism in humans [179] suggesting a potential mechanism for neutralizing the eNOS-related anti-oxidant effects of L-arginine.

7.1.5. Flavonoids

Flavonoids are polyphenolic compounds commonly found in concentrated amounts in multiple fruits, vegetables, and beverages, including apples, berries, grapes, onions, pomegranate, red wine, tea, cocoa, and dark chocolate. The exact structure and composition of the flavonoid compounds varies between food sources, and flavonoid content can be altered based on the manner of food preparation [180]. Interest in flavonoids as antioxidants therapy for cardiovascular disease originates from epidemiological data suggesting improved cardiovascular outcomes in individuals with high intake of food and beverages with high flavonoid content as well as cellular work suggesting a strong anti-oxidant effect of these compounds [181]. However, the limited oral bioavailability of flavonoids suggests cells signaling mechanism, rather than free radical quenching activity, is more likely to be root of sustained cardiovascular benefits from flavonoids [182, 183]. This concept is consistent with studies demondtrating that flavonoids can inhibit NADPH oxidase through ACE inhibition, increase eNOS-specific NO production through the estrogen receptor, and alter COX-2 expression [184]. Studies investigating the anti-hypertensive effects of flavonoids are inconclusive. While multiple small studies of short duration of dark chocolate therapy have demonstrated blood pressure lowering effects in hypertensives [185], studies in normotensive and pre-hypertensive individuals have demonstrated no benefit [186], further tea intake may, at least temporarily, increase blood pressure certain populations [187, 188]. The specific flavonoids and combination of flavonoids that exert the largest beneficial effects remain unknown. The follow table indicates a function of antioxidants in therapy.

Selenium	Septic ICU patients; major burns in combination with Cu and Zn; trauma patients	Ceiling "/>750 µg/day?
Zinc	Pneumonia in children: clinical course significantly shortened	Immune depression if doses"/>50 mg7day are provided
Cu-Se-Zn	Burns: trials showing reduction of infectious complication (pneumonia) and improved wound healing	Doses were calculated to compensate for the exudative losses
Vitamin E (α-tocoferol)	SIRS enteral supplementation	Convincing animal data
Vitamin C (ascorbic acid)	Burns, megadose during the first 24 h after injury; trauma, combined with vitamin E	Possible an endothelial mechanism (189)

Table 2. Antioxidants more indicated in treatments degeneratives chronics.

8. Conclusions

The antioxidants present in food playing an important role in preventing chronic diseases. A balanced diet can prevent diseases associated with oxidative stress and help keep the body in top condition.

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